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EXAMINER	Yong Soo Chong
ART GROUP	1617
APPLICANT	Gordon W. Glazner
SERIAL NO:	09/878,918
FILED	June 13, 2001
FOR	THERAPEUTIC USES FOR IP3 RECEPTOR-MEDIATED CALCIUM CHANNEL MODULATORS

Commissioner of Patents
Washington, D.C., 20231
U.S.A.

Dear Sir:

DECLARATION UNDER 37 CFR 1.132

I, Gordon W. Glazner, Principal Investigator, Division of Neurological Disorders, St Boniface Research Centre, and Assistant Professor, Department of Pharmacology, University of Manitoba School of Medicine, 4052-351 Tache Ave, Winnipeg, Manitoba, Canada solemnly declare that:

1. I am the sole inventor of USSN 09/878,918, filed June 13, 2001 and entitled "Therapeutic uses for IP3 receptor-mediated calcium channel modulators".

2. The examiner has observed that Mayne et al performed work using XeC in a model in which one of the HIV coat proteins (TAT) was used to induce calcium release in neurons, and has concluded that this constitutes prior art concerning the use of XeC as a treatment for HIV infection. This conclusion is invalid for a number of reasons described in detail below.

3. The instant application specifically examines PBMCs which are infected with HIV. We are interested in examining the ability of XeC to inhibit HIV infection. The Mayne et al manuscript is concerned exclusively with examining calcium regulation in neurons. The only link to HIV is the use of a specific HIV coat protein which is known to induce intracellular calcium release. In other words, Mayne et al used an HIV coat protein as a pharmacological agent

to induce a specific second messenger system in neurons, and not as a model of HIV infection.

4. The instant application examines PBM cells, which are primary first-line cells to be infected by the HIV virus. Because we are specifically examining HIV infection, it is obvious that we must use a cell type that is susceptible to the HIV virus. Mayne et al were not interested in HIV infection at all, but were examining calcium release characteristics in neurons, and were merely using a special HIV protein to induce calcium release. It is critical to note that neurons are not susceptible to HIV infection, a fact that is well known to neuroscientists. Neurons were used in the Mayne et al manuscript because the authors had no interest in HIV infection, no interest in examining XeC as a treatment for HIV infection, and made neither comments nor conclusions concerning XeC as a treatment for HIV infection.

5. The instant application suggests that treatment with XeC may inhibit HIV infection by interfering with activation of NF-kB, which acts to block infected cells from entering the apoptotic cycle. In the Mayne et al manuscript, XeC was demonstrated in neurons to protect neurons from death caused by a specific HIV protein. This is important to understand. In our hands, and in our patent application, we show that whole HIV, during infection, activates NF-kB and thus blocks the cells from dying. Our theory and data show that XeC inhibits NF-kB and thus allows cells to commit cellular suicide. In the Mayne et al manuscript, the HIV coat protein they were examining induced cell death (opposite of whole HIV in PBMCs) and this was partially prevented by XeC (again, opposite from treatment of infected PBMCs). Thus, Mayne et al proposed XeC as a way of protecting neurons from cellular suicide caused by calcium release, while our data and proposal show that XeC can induce cellular suicide in PBMCs infected with HIV.

6. Pettit; Stingl and DeBarieri teach that XeD and XeE may be useful for treating certain retroviral infection (but not HIV). This has been used to argue that it would be an obvious logical step to assume XeC may be used to treat HIV. This makes two assumptions which, in this case, are not valid. XeC has been shown to be a highly specific inhibitor of IP3-mediated calcium release which is not true of XeD or XeE-though these are structurally related, the actions have not been shown to be equivalent. In fact, Gafni et al showed that only XeC demonstrated specific inhibition of IP3-mediated calcium release.

7. The other assumption, that all retroviruses might be expected to behave in a similar manner is also incorrect, as not all retroviruses activate NF-kB, and not all retroviruses which activate NF-kB require this transcription factor for survival.

8. Thus, XeC is significantly different in action than either XeD or XeE, and retroviruses have multiple strategies for infection.

9. I declare that all statements made therein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing therefrom.

Gordon W. Glazner

Patrick Jean-François ETESSE

14 - Sept - 06
Date

State of }
} SS
County of }

On this 14th day of September, 2006, before me personally appeared Patrick Jean-François ETESSE, to me known to be the person named in and who executed the above instrument, and acknowledged to me that he executed the same for the uses and purposes therein set forth.

Notary Public/Witness

Joost VERBURG

6 - Sept - 06
Date

State of }
} SS
County of }

On this 5th day of September, 2006, before me personally appeared Joost VERBURG, to me known to be the person named in and who executed the above instrument, and acknowledged to me that he executed the same for the uses and purposes therein set forth.

Notary Public/Witness

Philip John PORTER

17th August 2006
Date

State of }
} SS
County of }

On this 17th day of August, 2006, before me personally appeared Philip John PORTER, to me known to be the person named in and who executed the above instrument, and acknowledged to me that he executed the same for the uses and purposes therein set forth.

Notary Public/Witness

REVISED: 23 June 2006